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Adverse events associated with intravenous phenytoin in children: a prospective study

RICHARD E. APPLETON[†] & ANDREA GILL[‡]

[†]*The Roald Dahl EEG Unit, Departments of Neurology and* [‡]*Pharmacy, Royal Liverpool Children's Hospital (Alder Hey), Liverpool, UK*

Correspondence to: Richard Appleton, The Roald Dahl EEG Unit, Department of Neurology, Royal Liverpool Children's Hospital (Alder Hey), Liverpool L12 2AP, UK. *E-mail*: richard.appleton@rlch-tr.nwest.nhs.uk

A prospective study was undertaken to assess the type and frequency of adverse side-effects following the use of intravenous phenytoin in children. Twenty-two children received a total of 100 doses over a 10-month period. Six patients (27%) experienced one or more side-effects, including extravasation of the drug, hypotension and cardiac arrhythmia. No patient developed skin necrosis, including the 'purple glove syndrome'. Recovery from all adverse side-effects was spontaneous and complete. It is possible that some or all of these side-effects may have been caused by an excessive rate of infusion of phenytoin or the saline 'flush' following administration of the drug. The overall frequency of side-effects was perhaps less than expected.

Key words: phenytoin; intravenous; adverse events; purple glove syndrome; children.

INTRODUCTION

Phenytoin has been used in the management of epilepsy for over half a century. Together with intravenous (i.v.) phenobarbitone, i.v. phenytoin remains one of the preferred long-acting anti-convulsant drugs in treating convulsive (tonic–clonic) status epilepticus[1]. The primary advantage of phenytoin compared to phenobarbitone is that it is not associated with any significant sedation or respiratory difficulties. However, i.v. phenytoin may induce hypotension and cardiac arrhythmias if infused too quickly and may also cause tissue necrosis, including the 'purple glove syndrome' (PGS)[2–7], if extravasation occurs at the site of i.v. cannulation. Despite these potentially serious adverse events, it is somewhat surprising that they have been the subject of relatively few published reports. It is possible that this may simply reflect an under-reporting of these side-effects[8,9].

Fosphenytoin is a recently introduced pro-drug of phenytoin, which being water soluble rather than lipid soluble (as is phenytoin) may be administered more rapidly and it is also reported to be associated with a far lower risk of causing tissue necrosis and pain when there is extravasation of the drug[10,11]. However, there are very few paediatric data[12] on this reportedly lower complication rate of fosphenytoin and, importantly, the current cost of fosphenytoin is at least fivefold greater than that of phenytoin.

The objective of this survey was to prospectively describe the incidence of adverse side-effects associated with the use of i.v. phenytoin in an attempt to evaluate the frequency and extent of the risks of its use and, consequently, to potentially support the justification for replacing this drug with fosphenytoin.

PATIENTS AND METHODS

Data collection forms were designed, piloted and subsequently distributed to all clinical areas in the hospital where i.v. phenytoin was being used. These areas included all the medical and surgical wards, the Accident & Emergency (A & E department) and the paediatric intensive care unit (PICU) in a large Children's Teaching Hospital. Nursing and medical staff in the clinical areas were instructed on the purpose of this study and how to record the data on the study forms and subsequently asked to complete a data collection form for every dose of i.v. phenytoin administered over the study period.

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Demographic data were collected on the following: the patient's age and sex; dose of phenytoin; rate of phenytoin infusion and rate of 'flush' following the administration of phenytoin and possible/probable adverse events following each dose. The specific adverse events that were recorded included the following: erythema at the site of an injection, pain at the site of the injection, incidence of the 'PGS', whether the i.v. cannula required re-siting, whether the prescribed dose of phenytoin had to be administered again because of prematurely terminating the infusion because of any local or systemic adverse event, and whether the patient developed hypotension or any cardiac arrhythmia (as identified on continuous electrocardiographic monitoring) during the infusions. Information was not collected on the weight and height of the patient, the clinical indication for administering phenytoin and blood levels of phenytoin.

RESULTS

Twenty-two patients (12 male) were administered 100 separate doses of i.v. phenytoin during the 10-month study period. Phenytoin was administered in seven clinical areas including the A & E department, the PICU, four medical wards and the neonatal surgical unit. The patients ages ranged from 0.5 to 14.2 years with a median age of 5.2 years. Sixty-one doses of phenytoin were administered in the PICU, 38 in the four medical and one surgical wards, and one in the A & E department.

In 88 exposures, the i.v. cannula was placed in the upper limb (antecubital fossa or dorsum of the hand); in 12 the cannula was inserted in the lower limb (dorsum of foot or femoral vein within the groin). The size of the peripheral i.v. cannula or butterfly needle was 20–22 gauge in all 39 non-PICU doses. Approximately, 75% of the doses administered in PICU were through a central venous line but the precise gauge of needle used in the remaining 25% of the peripheral venous cannulations was not recorded.

Saline (0.9%) 'flushes' following the infusion of phenytoin were used in all 100 doses.

Six patients (27%) experienced an adverse event that was considered to be directly related to the infusion of i.v. phenytoin, including extravasation and cutaneous infiltration (three patients), occlusion of the peripheral i.v. line (two patients), hypotension (one patient) and cardiac arrhythmia (tachycardia, (one patient)). One patient experienced two adverse events (drug extravasation and peripheral vein occlusion). The episodes of hypotension and cardiac arrhythmia resolved spontaneously within 30 minutes of discontinuing the infusion of phenytoin. Seven of the 100 doses exceeded the minimum recommended infusion rate of 20 minutes. Forty-eight doses were 'flushed' more rapidly than the recommended infusion rate of 20–30 minutes (the recommendations are based on the drug's data sheet and local pharmacy guidelines). These excessive rates of infusion (of either the phenytoin or the subsequent, saline 'flush') could potentially have explained the two episodes of hypotension and cardiac arrhythmia. No patient developed either the 'PGS' or demonstrated any significant skin discoloration or ulceration at the site of the i.v. cannulation, including the four patients who experienced extravasation of the drug and/or occlusion of the peripheral venous line. Two patients complained of transient discomfort and pruritis at the cannulation site (both cannulae sited in the dorsum of the hand), which did not necessitate discontinuing the phenytoin infusion and which resolved on completion of the phenytoin infusion. The two patients who developed peripheral vein occlusion required insertion of replacement i.v. cannulae and one of these two patients also had the dose of phenytoin repeated. No additional interventions or replacement cannulae or repeat drug infusions were required in the remaining 20 patients or 98 doses. The patient who developed the cardiac arrhythmia was resident on the PICU; the other five patients were on one of the medical wards. One of these patients was a 15-year-old boy with severe learning and behaviour difficulties who experienced both extravasation of phenytoin and occlusion of a peripheral cannula, complications that were felt to possibly reflect his impaired understanding and co-operation with procedures.

The doses of i.v. phenytoin were between 18 and 20 mg/kg/dose for all loading doses and between 3 and 6 mg/kg/dose for all maintenance doses; all maintenance doses were given on the basis of a twice daily dosing regime. All adverse events occurred in patients receiving maintenance doses of phenytoin.

DISCUSSION

This study has demonstrated that the use of i.v. phenytoin in children may be associated with potentially serious side-effects, with over one quarter of the patients reporting at least one adverse event. Four patients experienced a local complication with either occlusion of a peripheral vein or extravasation into the skin but without any local erythema, ulceration or development of 'PGS'. Two other patients experienced a systemic complication that was considered to be related to an excessive rate of infusion of either phenytoin or the subsequent saline 'flush'. All local and systemic complications were transient and other than requiring the insertion of new i.v. cannulae in two patients, resolved spontaneously. The patients otherwise required no additional interventions or procedures (and, therefore, no

additional expense) as a direct consequence of these adverse events. Only one patient required a repeat dose of phenytoin, following occlusion of the peripheral cannula.

As far as we are aware, all phenytoin doses were 'captured' and, therefore, surveyed during the study period, by cross-checking ward supplies and pharmacy records. However, it is possible that some doses may have been missed, although these are likely to represent a very small number.

The local and systemic complications of i.v. phenytoin have been recognised for many years[2]. The specific local complication of the 'PGS' (oedema, discoloration and pain, distal to the site of the i.v. administration of the drug) has been the focus of most previous reports[2–7], including a recent prospective study[7]. In this study of 157 adult patients (receiving a total of 179 doses), two patients (three doses; 1.7%) developed 'PGS' but there was no report of other, less serious local complications and no comment on any systemic, cardiovascular adverse events[7].

Although phenytoin is a weak organic acid, its vehicle or carrier is highly alkaline (pH 12) and is poorly soluble at a neutral pH. Ethanol and propylene glycol are added to phenytoin and its carrier (sodium hydroxide) to enhance its solubility and these compounds are highly irritating to soft tissue and may result in tissue necrosis if there is extravasation of the drug[1]. Fosphenytoin is a pro-drug of phenytoin that is both water soluble and uses a vehicle that is less toxic than phenytoin (pH 8.6–9)[10]. As a result it is considered to be associated with fewer local complications, including specifically, the 'PGS'. An additional reported benefit of i.v. fosphenytoin is its safer cardiovascular profile with a far lower risk of inducing hypotension and cardiac arrhythmias[10, 12, 13]. However, this early optimism may have been somewhat premature following a report by the Committee on Safety of Medicines (CSM) in the UK of serious arrhythmias and hypotension following the infusion of fosphenytoin at the 'recommended' infusion rates[14]. There are two additional disadvantages of using i.v. fosphenytoin, one of which is potential and the other real. The potential disadvantage is that because the dosing of this drug is in 'phenytoin equivalents' this may result in potential confusion and prescribing errors, resulting specifically in administering higher than intended doses. The other, and real disadvantage is that as of late 2002, for equivalent dosing, i.v. fosphenytoin costs at least five times that of phenytoin.

A number of reports have been published that have attempted to justify the increased cost of using fosphenytoin on the basis of the potential complication rate and frequency of adverse events with phenytoin and specifically the costs incurred in treating these adverse events[8, 15, 16]. These costs may potentially range from replacing a single i.v. cannula, the use of dressings and antibiotics to treat any local skin ulceration and secondary infection, the funding of acute resuscitation and treatment (including intensive care) for treating hypotension and cardiac arrhythmias, the use of plastic surgery in treating the 'PGS' to expensive legal costs arising from either the excessive dosing of phenytoin or an inappropriate rate of infusion. Clearly, many if not most of these costs are hypothetical rather than actual and generally, this pharmaco-economic argument is somewhat artificial. One could reasonably argue that because the local and systemic side-effects of i.v. phenytoin are well recognised, as are the guidelines and recommendations as to how the drug should be administered, there should, therefore, be a low risk (and incidence) of serious adverse events. The results of the present study would lend some support to this argument. In addition, one could reasonably have expected that the frequency of local adverse events (including specifically the 'PGS') would have been greater because of the smaller diameter of children's veins and the difficulties in cannulating these veins.

Although the numbers in this prospective study are relatively small, it is unlikely that the results could be used to support or justify the replacement of i.v. phenytoin with i.v. fosphenytoin in routine paediatric practice.

Finally, in the United States, the branded or proprietary form of i.v. phenytoin (Dilantin®), has now been withdrawn by Parke-Davis and replaced with its branded formulation of fosphenytoin, (Cerebyx®) At the time of writing, Parke-Davis is not planning to withdraw its UK proprietary formulation of phenytoin, (Epanutin® Ready-mixed Parenteral; personal communication).

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